Article

Premorbid Speech and Language Impairments in Childhood-Onset Schizophrenia: Association With Risk Factors

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Objective: As both premorbid neurodevelopmental impairments and familial risk factors for schizophrenia are prominent in childhood-onset cases (with onset of psychosis by age 12), their relationship was examined.

Method: Premorbid language, motor, and social impairments were assessed in a cohort of 49 patients with childhood-onset schizophrenia. Familial loading for schizophrenia spectrum disorders, familial eye-tracking dysfunction, and obstetrical complications were assessed without knowledge of premorbid abnormalities and were compared in the patients with and without developmental impairments.

Results: Over one-half of the patients in this group had developmental dysfunction in each domain assessed. The patients with premorbid speech and language impairments had higher familial loading scores for schizophrenia spectrum disorders and more obstetrical complications, and their relatives had worse smooth-pursuit eye movements. The boys had more premorbid motor abnormalities, but early language and social impairments did not differ significantly between genders. There were no other significant relationships between premorbid social or motor abnormalities and the risk factors assessed here.

Conclusions: Premorbid developmental impairments are common in childhood-onset schizophrenia. The rates of three risk factors for schizophrenia (familial loading for schizophrenia spectrum disorders, familial eye-tracking dysfunction, and obstetrical complications) were increased for the probands with premorbid speech and language impairments, suggesting that the pathophysiology of schizophrenia involves the abnormal development of language-related brain regions.

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Consistent with the neurodevelopmental hypothesis of schizophrenia (1, 2), premorbid dysfunction has been well documented in patients with the disorder (3, 4). Children and adolescents who later develop schizophrenia as adults have higher than expected rates of abnormal speech and motor development, poorer social development, lower intelligence, and worse educational performance (5–12).

Aberrant neurodevelopment may be even more salient in cases of schizophrenia with very early onsets (13). Childhood-onset schizophrenia (onset of psychosis by age 12) is a severe illness that is clinically and neurobiologically continuous with the adult disorder (14, 15). Although the rarity of childhood-onset schizophrenia has limited studies of such patients' premorbid development, there is suggestive evidence that premorbid dysfunction may be heightened in patients with a very early onset of the disorder. Kolvin and colleagues (16) reported a high rate of developmental delays (49%), largely involving language, and premorbid "oddities" (mostly social withdrawal and isolation) (87%) in a group of 33 patients who developed schizophrenia between ages 5 and 15. Later studies (17–21) showed similarly high rates of speech and language, motor, and social impairments in patients with childhood-onset schizophrenia. Taken together, these studies suggest that the rate of early impairments in patients with childhood-onset schizophrenia is higher than that for patients with an onset in adulthood (17–21).

In the current study we examined the relationship between premorbid developmental characteristics of patients with childhood-onset schizophrenia and familial and obstetrical risk factors for the disorder. Given the preliminary evidence for high rates of premorbid dysfunction and familial risk factors for schizophrenia in these patients (15), we anticipated significant associations between inherited markers of risk for the disorder (familial schizophrenia spectrum disorders and eye-tracking dysfunction) and premorbid impairments. As the rate of obstetrical complications does not seem to be increased for patients with childhood-onset schizophrenia (22), we did not predict significant associations between premorbid dysfunction and pre- and perinatal complications.

Method

Subjects

Since 1991, 49 patients (29 boys, 20 girls) have participated in a comprehensive study of childhood-onset schizophrenia (14). The diagnosis of schizophrenia was made according to DSM-III-R criteria with good reliability (kappa=0.77 [23]) by two child psychiatrists using clinical and structured interviews, including the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (24).

This study was approved by the Institutional Review Board of the National Institute of Mental Health (NIMH). After complete description of the study, written informed consent was obtained from the parents or legal guardians of the subjects. All patients gave written assent for their participation.

Assessment of Premorbid Development

In accord with the method of Hollis (20), case notes, including the original pediatric, psychiatric, psychological, and educational assessments, were examined by one of the authors (S.S.), blind to other risk factors, to determine the presence of premorbid speech and language, motor, and social impairments. To limit the possibility of a recall bias, these premorbid reports (completed by the relevant professional at the time of the original assessment) were supplemented by parental recall only in the rare instances in which it was needed to clarify or confirm a premorbid abnormality.

The language abnormalities noted included articulation or rhythm abnormalities, receptive language problems, or expressive language dysfunction (including delayed milestones). The motor impairments assessed were delayed milestones (not included by Hollis [20] but included here on the basis of evidence for delayed motor milestones in patients with schizophrenia [6]), abnormal repetitive movements, and clumsiness or poor coordination. The evidence of premorbid social dysfunction included abnormal peer relationships, isolation or withdrawal, and social disinhibition.

Each broad area of impairment (language, motor, social) was scored as present or absent. An abnormality was scored as present only if it was mentioned as an area of concern in the patient's record before the onset of the prodromal or psychotic symptoms. For example, evidence of an expressive language abnormality could include the results of a speech pathology assessment and a referral for speech therapy based on these results. Similarly, clumsiness would be scored as present if teachers and/or occupational therapists indicated that the child lacked coordination, and teachers' comments that a child was isolated and lacked friends would lead to a positive score for social isolation. A subset of these records (N=12) was rated independently by two of the authors (S.S., P.G.) with good reliability (kappa=1.0, 0.82, and 0.82 for the presence of language, motor, and social abnormalities, respectively).

Using this method, Hollis (20)demonstrated that patients with an onset of schizophrenia before age 18 had more premorbid language, motor, and social impairments than a matched group of nonpsychotic psychiatric comparison subjects. In addition, the patients whose schizophrenia began by age 13 had a higher rate of premorbid language dysfunction than did the schizophrenic patients with onsets between ages 14 and 17. Within the NIMH group, 13 of the patients with childhood-onset schizophrenia had undergone testing with the Wechsler Intelligence Scale for Children (WISC) before the onset of their psychotic symptoms. Further evidence of the validity of the measures of premorbid functioning used here is the fact that the subjects rated by us as having premorbid language impairments had a nonsignificant trend toward lower raw scores on the language-related items (comprehension, similarities, and comprehension) of the WISC than did the subjects without premorbid language impairments (t=1.9, df=11, p=0.08). As well, among the 47 patients in this cohort who completed intelligence testing at the time of their entrance into this study (two were unable to complete the testing because of their clinical conditions), those determined to have premorbid abnormalities of speech and language also had lower scores on the same language-related WISC items (t=2.0, df=45, p=0.05).

Assessment of Risk Factors for Schizophrenia

Familial psychopathology. To assess the presence of schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder, schizotypal personality disorder, paranoid personality disorder), 132 (92.3%) of 143 first-degree relatives over age 5 were interviewed by using the Schedule for Affective Disorders and Schizophrenia (25) and the Structured Interview for DSM-IV Personality Disorders (26) (for relatives 18 years of age and over; N=114) or the Diagnostic Interview for Children and Adolescents (27) (for relatives under age 18; N=18). The remainder could not be located (N=4), refused to participate (N=3), had a level of mental retardation that precluded participation (N=3), or were deceased (N=1). All interviews were done without knowledge of the proband's premorbid development.

To classify each proband's level of familial loading for schizophrenia spectrum disorders, the familial loading score devised by Verdoux and colleagues (28) was used, although modifications were made in order to take into account differences in this cohort. As "affected relatives" were defined here as those with schizophrenia spectrum disorders, the lifetime risks for the relatives of probands with familial and sporadic illness were different from those suggested in the original formula (28). On the basis of the results of the Roscommon Family Study (29–31), we assumed the lifetime risk for a relative of a proband with familial schizophrenia to be 17% and that for a relative of a proband with sporadic schizophrenia to be 3%. Given the fact that this cohort was selected for very early onset, the age of risk was assumed to be 10 to 50 rather than the 15 to 50 suggested by Verdoux et al. (28). Therefore, the ratio for the likelihood that a proband will have familial or sporadic schizophrenia, given that a relative of age X is affected, is

$$[0.17(X-10)/(50-10)][0.03(X-10)/(50-10)] = 5.7,$$

while if a relative of age X is unaffected, the likelihood ratio is

$$\{1-[0.17(X-10)/(50-10)]\} \div \{1-[0.03(X-10)/(50-10)]\}.$$

The likelihood ratio was calculated for each relative, and an overall likelihood ratio indicating whether each proband had familial or sporadic schizophrenia was determined by multiplying the individual likelihood ratios for all interviewed relatives. Finally, as the results were highly skewed, the logarithm of the product was determined.

Familial eye-tracking dysfunction. A smooth-pursuit eye movement task was completed by 89 first-degree relatives over the age of 13. The degree of eye-tracking dysfunction was assessed qualitatively by one of the authors (R.N.), blind to patient identity, by using a scale of 1 (best) to 5 (worst) with exemplars presented by Shagass and colleagues (32), and the mean score for the relatives of each proband was determined. Eye blinks and periods when the subjects were not tracking were not included in the assessment. Two of the authors (R.N., G.K.T.) rated a subset of this sample (N=10) with high reliability (intraclass correlation coefficient=0.98).

Proband pre- and perinatal complications. Original birth records of 36 probands were obtained; the remainder had been destroyed by the hospitals where the births had occurred. The available records were assessed without knowledge of patient identity by two of the authors (J.N.G., D.M.) to determine the

TABLE 1. Presence of Premorbid Impairments and Risk Factors for Schizophrenia in Patients With Childhood-Onset Schizophrenia

Patient	Sex	Premorbid Developmental Impairment[a]			Score for Familial Loading for Schizophrenia Spectrum Disorders[b]	Mean Family Score for Eye Tracking[c]	Number of Obstetrical Complications[d]
		Language	Motor	Social			
1	M	No	Yes	Yes	–0.11	1.35	0
2	M	No	Yes	No	–0.10	2.25	0
3	F	No	No	No	0.66	—	0
4	F	Yes	No	Yes	0.72	4.40	1
5	M	No	Yes	No	–0.16	1.80	0
6	M	No	No	No	–0.06	2.80	0
7	F	Yes	No	Yes	–0.11	—	0
8	M	Yes	Yes	Yes	–0.16	1.93	0
9	M	Yes	Yes	Yes	2.19	2.15	0
10	F	No	No	No	–0.14	1.85	—
11	M	No	Yes	Yes	–0.06	—	—
12	F	No	No	No	—	—	—
13	F	Yes	No	No	–0.06	2.40	—
14	M	No	No	No	0.69	1.33	0
15	F	No	No	No	–0.13	2.50	0
16	M	Yes	Yes	Yes	–0.12	2.45	1
17	M	No	Yes	No	–0.17	2.67	—
18	F	Yes	No	No	0.69	2.95	—
19	M	Yes	No	Yes	0.72	—	—
20	M	Yes	Yes	No	1.47	3.27	2
21	F	Yes	Yes	Yes	1.51	—	0
22	F	No	No	Yes	–0.08	2.10	—
23	M	Yes	Yes	Yes	0.70	2.80	1
24	F	No	Yes	Yes	–0.13	1.20	—
25	F	No	Yes	No	–0.15	3.25	—
26	M	Yes	Yes	Yes	0.68	2.37	0
27	M	Yes	No	No	–0.12	3.17	1
28	F	Yes	Yes	Yes	0.66	1.48	0
29	M	No	No	No	–0.16	2.37	0
30	F	Yes	No	Yes	0.70	1.80	1
31	M	No	Yes	Yes	0.76	—	0
32	M	Yes	No	Yes	–0.12	2.70	0
33	M	Yes	Yes	Yes	–0.15	1.90	0
34	F	Yes	Yes	Yes	–0.13	2.30	0
35	F	Yes	Yes	Yes	0.62	1.43	1
36	M	No	Yes	Yes	–0.07	—	0
37	M	No	Yes	No	0.66	1.70	1
38	F	Yes	No	No	0.62	2.70	0
39	F	Yes	Yes	Yes	0.65	2.33	—
40	F	Yes	No	No	0.72	2.90	0
41	M	Yes	Yes	Yes	0.71	3.35	—
42	F	No	No	No	–0.11	2.15	—
43	M	No	Yes	No	–0.14	2.30	0
44	M	Yes	Yes	Yes	0.71	—	2
45	M	No	No	No	3.00	2.13	0
46	M	Yes	Yes	Yes	0.70	—	0
47	M	Yes	Yes	No	–0.15	1.85	1
48	M	Yes	Yes	Yes	–0.14	2.60	0
49	M	No	No	Yes	–0.07	1.60	0

[a] Determined by using scale of Hollis (20).
[b] Determined by method of Verdoux et al. (28); see text.
[c] Mean qualitative rating (1=best, 5=worst) of relatives' performance on a smooth-pursuit eye movement task. Abnormal eye tracking was defined as a mean score of 2.5 or higher.
[d] As defined by Buka et al. (33).

number of obstetrical complications as defined by Buka and colleagues (33). The reliability for the presence of any obstetrical complication was good (kappa=0.77), and any discrepancies were resolved by consensus of the raters.

Statistical Analysis

The patients with and without premorbid developmental impairments in each area assessed (speech and language, motor, social) were compared by using t tests (family eye-tracking score), Mann-Whitney U tests (for variables with values not distributed normally: familial loading score, number of obstetrical complications), or chi-square tests (for binary variables: gender). A significance level of 0.05 (two-tailed) was set for all analyses, which were performed by using SPSS for Windows, version 9.0.

Results

Premorbid Development

Within this group of 49 patients, 28 (57.1%) had premorbid motor impairments, 27 (55.1%) had deviant social development, and 27 (55.1%) had premorbid speech and

TABLE 2. Relation of Premorbid Impairments to Schizophrenia Risk Factors for 49 Patients With Childhood-Onset Schizophrenia

Premorbid Impairment and Risk Factor	Premorbid Impairment Present			Premorbid Impairment Absent			Analysis		
	N	Mean	SD	N	Mean	SD	Test Statistic	df	p
Speech and language impairment[a]									
Sex							χ^2=0.3	1	0.57
Male	15			14					
Female	12			8					
Score for familial loading for schizophrenia spectrum disorders[b]	27	0.5	0.6	21	0.2	0.7	U=184.5		0.04
Mean family score for eye tracking[c]	22	2.5	0.7	17	2.1	0.6	t=2.1	37	0.04
Number of obstetrical complications[d]	22	0.5	0.7	14	0.1	0.3	U=101.0		0.03
Motor impairment[a]									
Sex							χ^2=6.8	1	0.009
Male	21			8					
Female	7			13					
Score for familial loading for schizophrenia spectrum disorders[b]	28	0.4	0.6	20	0.4	0.7	U=248.0		0.50
Mean family score for eye tracking[c]	22	2.2	0.6	17	2.5	0.7	t=1.2	37	0.25
Number of obstetrical complications[d]	22	0.4	0.7	14	0.2	0.4	U=135.0		0.43
Social impairment[a]									
Sex							χ^2=0.4	1	0.56
Male	17			12					
Female	10			10					
Score for familial loading for schizophrenia spectrum disorders[b]	27	0.4	0.6	21	0.3	0.8	U=214.5		0.15
Mean family score for eye tracking[c]	19	2.2	0.8	20	2.4	0.5	t=0.9	37	0.37
Number of obstetrical complications[d]	21	0.3	0.6	15	0.3	0.6	U=155.5		0.94

[a] Determined by using scale of Hollis (20).
[b] Determined by method of Verdoux et al. (28); see text.
[c] Mean qualitative rating (1=best, 5=worst) of relatives' performance on a smooth-pursuit eye movement task. Abnormal eye tracking was defined as a mean score of 2.5 or higher.
[d] As defined by Buka et al. (33).

language abnormalities. Among the 27 patients with abnormal speech and language development, 10 patients had premorbid speech impairments while 25 had early language abnormalities. Consistent with data indicating that language disorders are associated with a worse outcome than are speech impairments (34) was our observation that only two patients had speech impairments in the absence of other language dysfunction.

Further evidence of the difficulties experienced by these 49 patients years before the onset of their illness was the rate of delayed school entry or repeated grades (N=24, 49.0%) and the number of patients requiring special education (N=15, 30.6%). Table 1 shows the premorbid impairments and the risk factor profile for each patient.

Risk Factors for Schizophrenia

Familial psychopathology. Of the 132 relatives assessed by diagnostic interview, 29 were diagnosed with a schizophrenia spectrum disorder (15). Using a hierarchical method to assign diagnoses (35), we found that three had schizophrenia or schizoaffective disorder, 13 had schizotypal personality disorder, and 13 had paranoid personality disorder.

Familial eye-tracking dysfunction. Of the 89 relatives who completed the smooth-pursuit eye movement task, 35 (39.3%) had abnormal eye tracking (defined a priori as a mean score of at least 2.5) (15). There was no significant difference in the age of the relatives with normal and abnormal eye tracking (t=0.7, df=87, p=0.47), and the relatives with schizophrenia spectrum disorders did not have poorer eye tracking (t=0.2, df=86, p=0.81).

Proband obstetrical complications. Among the 36 patients for whom original birth records were available, 10 had obstetrical complications, a rate that did not differ significantly from that for sibling comparison subjects (22).

Relation of Premorbid Development to Risk Factors

As can be seen in Table 2, gender, familial psychopathology, and familial eye-tracking dysfunction showed significant relationships with at least some aspect of the probands' premorbid development. Patients with premorbid speech and language impairments had significantly greater familial loading for schizophrenia spectrum disorders, higher family eye-tracking scores, and more obstetrical complications (Table 2, top). There was no gender difference between the patients with and without premorbid language problems.

Significantly more boys than girls had premorbid motor abnormalities, but the patients with such motor problems did not have higher familial loading scores, worse familial eye tracking, or more obstetrical complications (Table 2, middle). The patients with premorbid social impairments did not differ from those without social problems in terms of gender, familial loading, familial eye tracking, or number of obstetrical complications (Table 2, bottom).

For the patients with family histories of schizophrenia spectrum disorders, the rates of familial eye-tracking dysfunction (χ^2=0.3, df=1, p=0.61) and obstetrical complica-

tions (χ^2=2.2, df=1, p=0.14) were not higher than those for the patients with negative histories, and patients with obstetrical complications did not have higher rates of familial eye-tracking dysfunction than patients without such complications (χ^2=0.2, df=1, p=0.63). There was no difference in the rate of premorbid language impairments between the patients with and without relatives designated as having "odd speech" according to the Structured Interview for DSM-IV Personality Disorders (χ^2=0.9, df=1, p=0.35).

The male and female patients did not differ in familial loading score (U=260.5, N=48, p=0.75), family score for eye tracking (t=0.3, df=37, p=0.78), or number of obstetrical complications (U=133.5, N=36, p=0.86).

There were significant relationships among the premorbid impairments in these probands. The patients with premorbid social dysfunction had a higher rate of early speech and language (χ^2=8.7, df=1, p=0.003) and motor (χ^2=7.0, df=1, p=0.008) impairments. There was no significant difference in the rate of language abnormalities between the patients with and without motor difficulties (χ^2=0.8, df=1, p=0.36).

Discussion

In this cohort of patients with childhood-onset schizophrenia, premorbid developmental impairments were common and similar in frequency to the rates in other studies of childhood-onset schizophrenia (17, 18, 20, 21). Comparisons with studies of adult-onset schizophrenia are problematic because of the use of different methods and the different age of the historical material, but the results here and elsewhere (16–18, 20, 21) suggest that premorbid impairments may be more common among patients with childhood-onset than adult-onset schizophrenia.

It is important to recognize that these premorbid abnormalities are neither sensitive nor specific to schizophrenia. Similar impairments are seen in the early histories of patients who later develop severe mood disorders, although they are more pronounced in children and adolescents who later develop schizophrenia (36). Furthermore, the vast majority of patients with developmental impairments do not develop schizophrenia in adolescence or adulthood (34).

Within this group of patients with childhood-onset schizophrenia, the patients with premorbid speech and language impairments had greater familial loading for schizophrenia spectrum disorders, poorer familial smooth-pursuit eye movement, and more obstetrical complications, all of which are risk factors for schizophrenia (37–39). No significant associations were found in these patients between the presence of any obstetrical complications, familial eye-tracking dysfunction, and schizophrenia spectrum disorders in relatives, suggesting that in this group, as in others (40, 41), these are independent risk factors for schizophrenia. The lack of association between premorbid speech and language impairments and "odd speech" in the home argues against the possibility that the probands' premorbid language dysfunction was due to a poor language environment, although it is possible that other aspects of familial environment might be related to the probands' early impairments.

Given the high rate of developmental speech and language disturbances in patients with schizophrenia and the high rate of the disorder in a study of adults who had had severe language abnormalities as children (34), premorbid language impairments may be an early manifestation of the neurodevelopmental abnormalities underlying schizophrenia. Moreover, the specific association between early language dysfunction and risk factors for schizophrenia found in our cohort of patients with a very early onset suggests that premorbid language impairments and some causal factors in schizophrenia may be mediated by aberrant neurodevelopment of the neural structures and circuits relevant to language.

The rate of obstetrical complications in this group of patients was not elevated above that for their siblings (22), and therefore, the high rate of obstetrical complications in the patients with premorbid language impairments was unexpected, although others (42) have found a relationship between pre- and perinatal complications and developmental language disorders.

While the expected higher rate of motor abnormalities among boys was noted, there was no significant gender difference in the rate of language or social dysfunction. It is possible that a lack of the protective factors normally associated with a lower rate of language disturbances in girls (42) may be related to the very early onset of schizophrenia for the female patients in this cohort.

The lack of association between premorbid motor impairments and familial loading for schizophrenia spectrum disorders was surprising given previous reports (43, 44) of developmental motor abnormalities in children of schizophrenic mothers. However, in a recent birth cohort study (11) the degree of familial loading for schizophrenia was not related to nonacademic performance (athletics and handicrafts). It may be that other nonspecific developmental abnormalities or the powerful gender effect on premorbid motor dysfunction in childhood-onset cases may outweigh the contribution of genetic factors in developmental motor dysfunction.

The limitations of this study include the small number of subjects, which was necessitated by the rarity of childhood-onset schizophrenia (23), and the lack of a healthy comparison group. As this was a study of patients with refractory schizophrenia, an ascertainment bias may also exist. Although the possibility of a recall bias cannot be excluded, the use of parental recall only when necessary to fill in missing information and the use of original case notes from pediatricians, mental health professionals, and schools limits this possibility. The assumption used in the formula for familial loading that the risk for spectrum personality disorders increases linearly with age may be in-

correct, although the fact that there was no age difference in the relatives of the patients with and without premorbid language impairments suggests that any artifact due to this assumption is unlikely to be of major importance. As well, the categorical rather than continuous description of premorbid impairments excludes, perhaps incorrectly, the possibility that impairments are distributed evenly throughout the population rather than existing discretely in some subjects.

In conclusion, patients with childhood-onset schizophrenia have a high rate of premorbid impairments. The association between risk factors for schizophrenia and premorbid speech and language dysfunction suggests that these risks may be mediated in part by aberrant neurodevelopment of language-related brain areas.

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References

1. Murray RM, Lewis SW: Is schizophrenia a neurodevelopmental disorder? Br Med J 1987; 295:681–682
2. Weinberger DR: Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987; 44:660–669
3. Davies N, Russell A, Jones P, Murray RM: Which characteristics of schizophrenia predate psychosis? J Psychiatr Res 1998; 32: 121–131
4. Ellison Z, van Os J, Murray R: Special feature: childhood personality characteristics of schizophrenia: manifestations of, or risk factors for, the disorder? J Personal Disord 1998; 12:247–261
5. Done DJ, Crow TJ, Johnstone EC, Sacker A: Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. Br Med J 1994; 309:699–703
6. Jones P, Rodgers B, Murray R, Marmot M: Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994; 344:1398–1402
7. Crow TJ, Done DJ, Sacker A: Childhood precursors of psychosis as clues to its evolutionary origins. Eur Arch Psychiatry Clin Neurosci 1995; 245:61–69
8. David AS, Malmberg A, Brandt L, Allebeck P, Lewis G: IQ and risk for schizophrenia: a population-based cohort study. Psychol Med 1997; 27:1311–1323
9. Isohanni I, Jarvelin MR, Nieminen P, Jones P, Rantakallio P, Jokelainen J, Isohanni M: School performance as a predictor of psychiatric hospitalization in adult life: a 28-year follow-up in the Northern Finland 1966 birth cohort. Psychol Med 1998; 28:967–974
10. Malmberg A, Lewis G, David A, Allebeck P: Premorbid adjustment and personality in people with schizophrenia. Br J Psychiatry 1998; 172:308–313
11. Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM: School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. Arch Gen Psychiatry 1999; 56: 457–463
12. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M: Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am J Psychiatry 1999; 156:1328–1335
13. Murray RM, O'Callaghan E, Castle DJ, Lewis SW: A neurodevelopmental approach to the classification of schizophrenia. Schizophr Bull 1992; 18:319–332
14. Jacobsen LK, Rapoport JL: Research update: childhood-onset schizophrenia: implications of clinical and neurobiological research. J Child Psychol Psychiatry 1998; 39:101–113
15. Nicolson R, Rapoport JL: Childhood-onset schizophrenia: rare but worth studying. Biol Psychiatry 1999; 46:1418–1428
16. Kolvin I, Ounsted C, Humphrey M, McNay A: Studies in the childhood psychoses, II: the phenomenology of childhood psychoses. Br J Psychiatry 1971; 118:385–395
17. Asarnow JR, Ben-Meir S: Children with schizophrenia spectrum and depressive disorders: a comparative study of premorbid adjustment, onset pattern and severity of impairment. J Child Psychol Psychiatry 1988; 29:477–488
18. Watkins JM, Asarnow RF, Tanguay PE: Symptom development in childhood-onset schizophrenia. J Child Psychol Psychiatry 1988; 29:865–878
19. Alaghband-Rad J, McKenna K, Gordon CT, Albus KE, Hamburger SD, Rumsey JM, Frazier JA, Lenane MC, Rapoport JL: Childhood-onset schizophrenia: the severity of premorbid course. J Am Acad Child Adolesc Psychiatry 1995; 34:1273–1283
20. Hollis C: Child and adolescent (juvenile onset) schizophrenia: a case control study of premorbid developmental impairments. Br J Psychiatry 1995; 166:489–495
21. Russell AT, Bott L, Sammons C: The phenomenology of schizophrenia occurring in childhood. J Am Acad Child Adolesc Psychiatry 1989; 28:399–407
22. Nicolson R, Malaspina D, Giedd JN, Hamburger S, Lenane M, Bedwell J, Fernandez T, Berman A, Susser E, Rapoport JL: Obstetrical complications in childhood-onset schizophrenia. Am J Psychiatry 1999; 156:1650–1652
23. McKenna K, Gordon CT, Lenane M, Kaysen D, Fahey K, Rapoport JL: Looking for childhood-onset schizophrenia: the first 71 cases screened. J Am Acad Child Adolesc Psychiatry 1994; 33:636–644
24. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980–988
25. Fyer AJ, Mannuzza SM, Klein DF, Endicott J: Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (SADS-LA). New York, New York State Psychiatric Institute, 1985
26. Pfohl B, Blum N, Zimmerman M: Structured Interview for DSM-IV Personality: SIDP-IV. Iowa City, University of Iowa, Department of Psychiatry, 1995
27. Reich W, Leacock N, Shanfeld K: Diagnostic Interview for Children and Adolescents (DICA-R). St Louis, Washington University, 1995
28. Verdoux H, van Os J, Sham P, Jones P, Gilvarry K, Murray R: Does familiality predispose to both emergence and persistence of psychosis? a follow-up study. Br J Psychiatry 1996; 168:620–626
29. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D: The Roscommon Family Study, I: methods, diagnosis of probands, and risk of schizophrenia in relatives. Arch Gen Psychiatry 1993; 50:527–540

30. Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'Hare A, Walsh D: The Roscommon Family Study, II: the risk of nonschizophrenic nonaffective psychoses in relatives. Arch Gen Psychiatry 1993; 50:645–652
31. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D: The Roscommon Family Study, III: schizophrenia-related personality disorders in relatives. Arch Gen Psychiatry 1993; 50:781–788
32. Shagass C, Amadeo M, Overton DA: Eye-tracking performance in psychiatric patients. Biol Psychiatry 1974; 9:245–260
33. Buka SL, Tsuang MT, Lipsitt LP: Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. Arch Gen Psychiatry 1993; 50:151–156
34. Rutter M, Mawhood L: The long-term psychosocial sequelae of specific developmental disorders of speech and language, in Biological Risk Factors for Psychosocial Disorders. Edited by Rutter M, Cesaer P. Cambridge, UK, Cambridge University Press, 1991, pp 233–259
35. Kendler KS: The impact of diagnostic hierarchies on prevalence estimates for psychiatric disorders. Compr Psychiatry 1988; 29:218–227
36. Jones PB, Tarrant CJ: Specificity of developmental precursors to schizophrenia and affective disorders. Schizophr Res 1999; 39:121–125
37. Kendler KS, Diehl SR: The genetics of schizophrenia: a current, genetic-epidemiologic perspective. Schizophr Bull 1993; 19:261–285
38. Levy DL, Holzman PS, Matthysse S, Mendell NR: Eye tracking dysfunction and schizophrenia: a critical perspective. Schizophr Bull 1993; 19:461–536
39. McNeil TF: Perinatal risk factors and schizophrenia: selective review and methodological concerns. Epidemiol Rev 1995; 17:107–112
40. Cantor-Graae E, McNeil TF, Sjostrom K, Nordstrom LG, Rosenlund T: Obstetric complications and their relationship to other etiological risk factors in schizophrenia: a case-control study. J Nerv Ment Dis 1994; 182:645–650
41. Keefe RS, Silverman JM, Mohs RC, Siever LJ, Harvey PD, Friedman L, Roitman SE, DuPre RL, Smith CJ, Schmeidler J, Davis KL: Eye tracking, attention, and schizotypal symptoms in nonpsychotic relatives of patients with schizophrenia. Arch Gen Psychiatry 1997; 54:169–176
42. Robinson RJ: Causes and associations of severe and persistent specific speech and language disorders in children. Dev Med Child Neurol 1991; 33:943–962
43. Fish B: Neurobiologic antecedents of schizophrenia in children: evidence for an inherited, congenital neurointegrative defect. Arch Gen Psychiatry 1977; 34:1297–1313
44. Marcus J, Hans SL, Auerbach JG, Auerbach AG: Children at risk for schizophrenia: the Jerusalem Infant Development Study, II: neurobehavioral deficits at school age. Arch Gen Psychiatry 1993; 50:797–809